REMARKS

After the above amendments, Claims 531-576 are pending.

The amendments to Claim 531 are intended only as clarifying amendments. Support for the amendments to Claim 531 may be found throughout the application, including page 7, line 10 through page 8, line 8; page 14, line 25 through page 16, line 5; page 19, line 14 through page 20, line 11; page 37, lines 17-25; and Examples 1 and 8-10 of the application.

Support for new Claims 574-576 may be found at page 40, lines 4-16, of the application. New Claims 574-576 have been added only to add additional dependent claims to more particularly claim certain subject matter.

A. Election/Restriction Requirements

With respect to the election of a specific peptide sequence covered by Claim 531, the Examiner states: "Applicants claim that all of the claimed peptides share a common property of binding metal ions, and also share a substantial structural feature of containing a histidine residue at the third amino acid position, thus would be obvious of each other if anyone [sic, any one] of the polypeptides is found in the prior art." Applicants did state that all of the peptides covered by Claim 531 bind metal ions and have histidine as the third amino acid in order to establish that the peptides are proper members of a Markush group. However, Applicants did not state, and do not admit, that any peptide covered by that claim would be obvious in view of any other peptide covered by the claim that was found in the prior art.

B. Information Disclosure Statements

The Examiner has deleted citations to certain references because they are references found on the internet. However, Applicants have provided the Examiner with printed copies of these references, so the references are available to the Examiner and should be available to anyone

requesting a copy of the file history of the application once a patent issues. Accordingly, the Examiner is hereby requested to consider these references and make them of record. Enclosed is a new PTO 1449 form listing these references without citations to the websites.

C. Objection To The Drawings

The Examiner has also pointed out an error in Figures 1A-1D. Applicants are submitting herewith an amended drawing of Figures 1A-1D to correct this obvious error.

D. Objection To The Claims

Claim 540 is objected because it does not include the sequence identifier of the sequence Asp Ala His Lys. However, it is not believed that the use of a sequence identifier is proper in this claim. First, the sequence could be composed of all L-amino acids, all D-amino acids or a combination of L- and D-amino acids, and sequence identifiers are required only for sequences composed of all L-amino acids. See 37 CFR § 1.821(a)(2) and Claims 555-557. Also, in Claim 540, P_2 could contain from 0-100 amino acids, and Asp Ala His Lys may not be the entire sequence. For all of the foregoing reasons, the Examiner is asked to withdraw this objection.

E. Objections To The Specification

The Examiner has asked that the cross references to related applications at the beginning of the application be updated to add the serial number of one of the provisional applications. By the above amendment of the specification, Applicants have done so.

On pages 6, 16 and 39, lines 9, 22-23, and 26, respectively, of the specification, the Examiner has asked that the embedded hyperlinks be deleted. By the above amendments, Applicants have deleted these hyperlinks.

F. Double Patenting Rejection

The Examiner has provisionally rejected Claims 531-571 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 83-118 of co-pending application Serial No. 10/186,168. This rejection is respectfully traversed, since Claims 83-118 of application Serial No. 10/186,168 have been canceled. Accordingly, the Examiner is asked to withdraw this rejection.

G. Section 112 Rejections

Claim 542 has been rejected as being indefinite for the use of the abbreviation "HMS". The Examiner is correct that HMS is the abbreviation for α-hydroxymethylserine. It is believed that the use of this abbreviation in Claim 542 is clear, since the meaning of HMS is given in the specification at line 27 on page 7.

Claims 556 and 557 have been rejected as being indefinite because they are improperly dependent on themselves. By the above amendments to these claims, the dependencies of these claims have been corrected.

Claims 556, 557 and 559 have been rejected as being indefinite because it is the Examiner's belief that another "or" needs to be inserted after the first variable. By the above amendments to Claims 556 and 559, an additional "or" has been inserted. It is not seen, however, that this issue is present in Claim 557.

Claims 560-562 and 569-573 have been rejected as being dependent on a rejected claim. Accordingly, the rejection of these claims should be withdrawn for the same reasons as given above.

H. Section 103 Rejections

1. Rejection of Claims 531-573

The Examiner has rejected Claims 531-573 as being unpatentable over Blaschuk et al. (U.S. Patent No. 6,610,821) in view of Sijmons et al. (U. S. Patent No. 5,650,307). Applicants respectfully traverse this rejection.

Blaschuk teaches that certain cyclic peptides, including Ac-Cys Ala His Ala Val Asp Cys, are modulators of cadherin-mediated endothelial cell adhesion (see column 3, line 5 through column 4, line 37). It is suggested that certain of the cyclic peptides would be of use in the inhibition of angiogenesis because of their ability to inhibit N-cadherin-mediated endothelial cell adhesion (see column 7, lines 37-42, column 9, line 45 through column 10, line 18, column 26, lines 24-67, and Example 3).

It is the Examiner's position that: "Claim 531 would . . . permit any substituent to be bonded to the α-amino group of Xaa_1." This is not correct. Although Xaa_1 can be substituted (see, *e.g.*, page 20, lines 3-11, of the present application), the α-amino group of Xaa_1 cannot be substituted. If this group is substituted, as by an acetyl group, the ability of the peptide to effectively bind metal ions is lost (see Example 10, especially Table 11, page 68, of the present application). Accordingly, Claim 531 has been amended to clarify that the α-amino group of Xaa_1 cannot be substituted.

Sijmons et al. describes the production of non-plant proteins and polypeptides in plants by genetic engineering techniques. Sijmons et al. is totally irrelevant and is not analogous art.

As can be readily seen from the foregoing, the Examiner has provided no teaching, suggestion or motivation for combining the teachings of Blaschuk with those of Sjimons. It is submitted that the only possible basis for combining the teachings of Blaschuk with those of Sijmons is improper hindsight reconstruction of the claimed invention by the Examiner using Applicants' disclosure as

a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner could not meet in this case.

Most important, however, the cited references, alone or in combination, do not teach or suggest the claimed method. Claim 531 is directed to a method of treating an angiogenic disease or condition in an animal by administering a metal-binding peptide of sequence P_1 - P_2 to the animal. The peptide P_1 - P_2 does not have metal ions bound to it so that it can bind metal ions present in the animal to thereby inhibit angiogenesis. This method of treating an angiogenic disease or condition by binding metal ions present in an animal using peptide P_1 - P_2 is not taught or suggested by Blaschuk or Sijmons et al., alone or in combination.

For all of the foregoing reasons, the Examiner is asked to withdraw this rejection.

2. Rejection of Claims 531-573

The Examiner has also rejected Claims 531-573 as being unpatentable over Yoshida et al. (*Neurosurgery*, **37(2)**:287-293 (1995)) in view of Harford and Sarkar (*Acc. Chem. Res.*, **30**:123-130 (1997)). It is the Examiner's position that:

> One would have been motivated to design a metal binding peptide as described in Harford and Sarkar, to chelate copper ions and inhibit angiogenesis as disclosed by Yoshida et al. to treat various angiogenic diseases or conditions, including neoplasms. Therefore, it would have been obvious to a person having ordinary skill in the art to administer a metal binding peptide to treat an angiogenic disease or condition (current application, claims 531-573).

Applicants respectfully traverse this rejection.

Harford and Sarkar describes a copper-binding motif found in certain proteins. This motif is referred to as the ATCUN motif, and the structural characteristics of this motif are described in Harford and Sarkar (see, *e.g.*, the Introduction). However, Harford and Sarkar also reports that,

although the ATCUN motif binds copper specifically, it can also release the metal easily with appropriate ligands, reflecting its role as a transport site in albumins (see, *e.g.*, the Introduction). As noted by the Examiner, the peptides of the present invention comprise an ATCUN motif.

Yoshida et al. describes a study of the effects of a combination of a copper-depletion diet and D-penicillamine (a copper chelator) on tumor growth and angiogenesis in a rat model (see Abstract and Materials And Methods section). This combined treatment is referred to as CDPT, and CDPT was found to produce a reduction in tumor weight and a reduction of vascular density in the tumors (see Abstract and Results section). The decrease in tumor growth was attributed to the suppression of angiogenesis by the CDPT (see Abstract). The only copper chelator investigated in Yoshida et al. was D-penicillamine.

It is noted in Yoshida et al. that some copper chelators inhibit angiogenesis and that other copper chelators stimulate angiogenesis (see the penultimate paragraph of column 1 on page 291). In particular, it is stated in this paragraph that: "More research and complex calculations relating to affinity and transfer kinetics are required to determine whether a carrier molecule becomes a stimulator of cell growth by delivering Cu or whether it becomes an inhibitor of cell growth by removing the bioactivity of the Cu ion."

Quite clearly, then, Yoshida et al. teaches that not all copper chelators would be expected to inhibit angiogenesis. Contrary to the Examiner's contentions, Yoshida et al. would not have created an expectation that any copper chelator (except D-penicillamine) would be effective in inhibiting angiogenesis or treating angiogenic diseases and conditions. Yoshida et al. is, at best, an invitation to experiment to determine which, if any, additional copper chelators would be effective in inhibiting angiogenesis.

Moreover, Yoshida et al. teaches away from using copper-binding compounds which deliver copper ions to sites of angiogenesis and which, therefore, would stimulate angiogenesis. Harford and Sarkar teach that ATCUN motifs are known to function to transport copper ions. Thus, Yoshida et al. teaches away from using peptides comprising an ATCUN motif.

Thus, based on the combined teachings of Yoshida et al. and Harford and Sarkar, those skilled would not have expected that peptides employing the ATCUN motif would inhibit angiogenesis or could be used to treat angiogenic diseases and conditions. More important, the combined teachings of Yoshida et al. and Harford and Sarkar would not have made the presently claimed invention obvious.

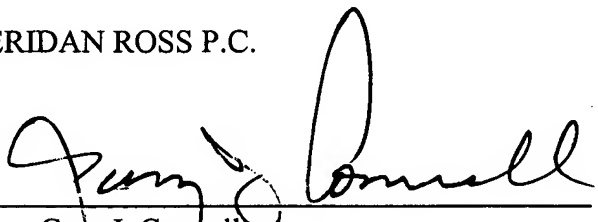
For the foregoing reasons, this rejection should be withdrawn.

CONCLUSION

It is respectfully submitted that the pending claims are in condition for allowance, and a speedy allowance of them is requested.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: 

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Date: Dec. 20, 2004

Amendments to the Drawings:

The attached drawing sheet includes changes to Figs. 1A - 1D. This sheet, which includes Figs. 1A - 1D, replaces the original sheet, in which the double bonds were missing from the imidazole group.

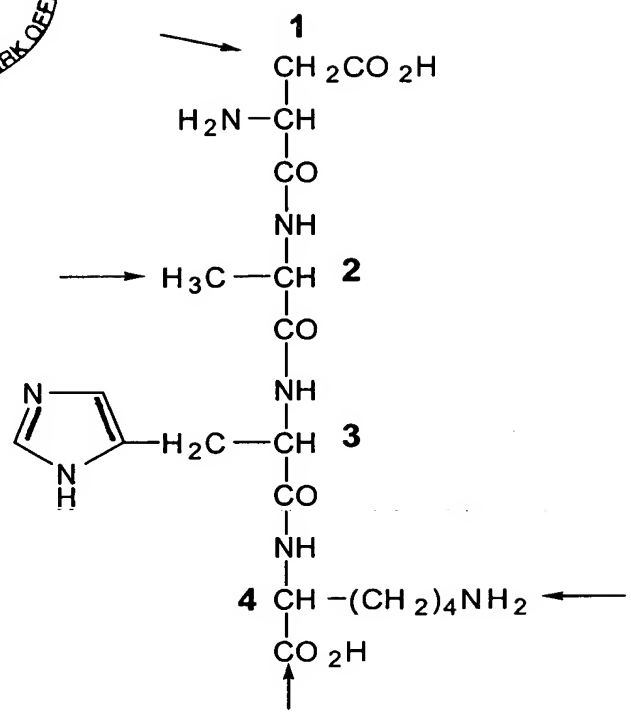

FIG. 1A

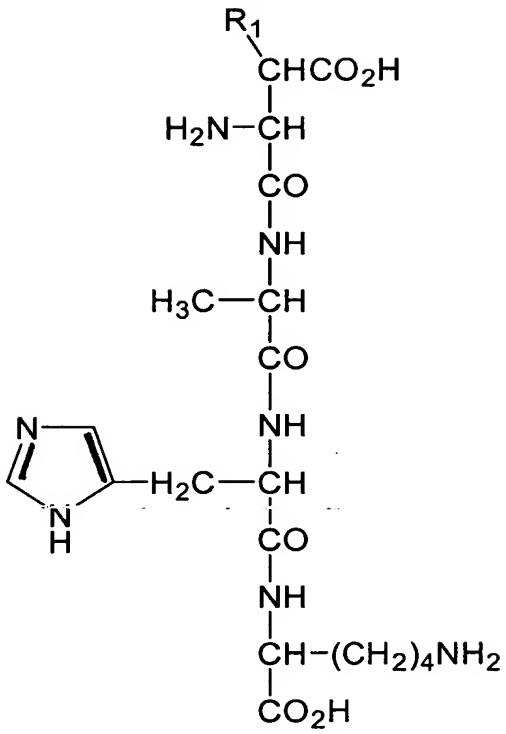

FIG. 1B

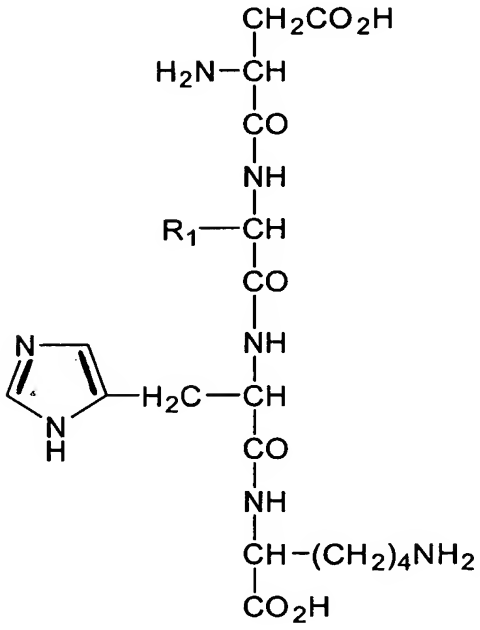

FIG. 1C

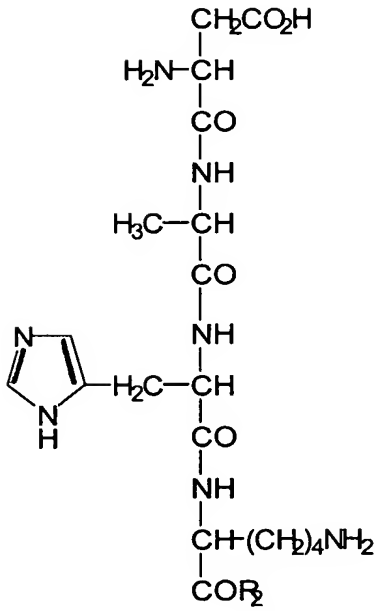

FIG. 1D